Please amend the above-identified application as follows:

## Amendments to the Claims:

*This listing of claims will replace all prior versions, and listings, of claims in the application:*

1. (previously presented) A method for recombinase mediated expression cassette exchange (RMCE) for substituting a positive-negative selectable marker by an incoming DNA in the genome of cells or parts of cells comprising the steps of

a) integrating into a chromosomal locus of the genome of said cells a first DNA expression cassette carrying a positive-negative selection marker flanked by a wild type FLP-recombinase recognition target (FRT) site on one end and a modified heterospecific FRT site on the other end,

b) selecting cell clones surviving the conditions for positive selection,

c) exchanging said first DNA expression cassette against an incoming second DNA expression cassette located on a circular vector and carrying a homologous or heterologous gene (transgene) of any coding sequence flanked by the same FRT sites as said first DNA expression cassette mediated by the action of FLP-recombinase,

wherein said cells are vertebrate embryonic stem cells (ES) and said parts of cells are nuclei of vertebrate cells, which can be inserted into ES cells, and wherein

d) maintaining the conditions for positive selection during cultivation of said cells obtained in step b) until exchanging said first DNA expression cassette against said incoming second DNA expression cassette,

e) using in step c) an incoming second DNA expression cassette which is marker-free, and

f) selecting cell clones obtained after step c) surviving the conditions for negative selection.

2. (original) The method according to claim 1 wherein said positive-negative selection marker is a hygromycin-B-phosphotransferase and HSV-thymidine kinase encoding (hygtk) fusion gene.

3. (previously amended) The method according to claim 1 wherein said modified heterospecific FRT site is a FRT spacer mutant.

4. (original) The method according to claim 3 wherein said FRT spacer mutant is the $F_3$ mutant.

5. (previously cancelled)

6. (previously amended) The method according to claim 1, wherein said vertebrate embryonic stem cells are mouse embryonic stem cells.

7. (previously amended) Regenerative vertebrate cells comprising a modified genome obtainable by the method of claim 1.

8. (previously amended) Nuclei of vertebrate cells comprising a modified genome obtainable by the method of claim 1.

9. (original) Regenerative vertebrate cells containing a nucleus according to claim 8.

10. (previously amended) A method for generation of transgenic mice comprising the step of injecting mouse ES cells comprising a modified genome obtained by the method of claim 1 into blastocysts of said mice.

11. cancelled.

12. (New) A method for recombinase mediated expression cassette exchange (RMCE) for substituting a positive-negative selectable marker by an incoming DNA in the genome of cells or parts of cells comprising the steps of

a) integrating into a chromosomal locus of the genome of said cells a first DNA expression cassette carrying a positive-negative selection marker flanked by a wild type FLP-recombinase recognition target (FRT) site on one end and a modified heterospecific FRT site on the other end, wherein said modified heterospecific FRT site is an $F_3$ spacer mutant,

b) selecting cell clones surviving the conditions for positive selection,

c) exchanging said first DNA expression cassette against an incoming second DNA expression cassette located on a circular vector and carrying a homologous or heterologous gene (transgene) of any coding sequence flanked by the same FRT sites as said first DNA expression cassette mediated by the action of FLP-recombinase,

wherein said cells are vertebrate embryonic stem cells (ES) and said parts of cells are nuclei of vertebrate cells, which can be inserted into ES cells, and wherein

d) maintaining the conditions for positive selection during cultivation of said cells obtained in step b) until exchanging said first DNA expression cassette against said incoming second DNA expression cassette

e) using in step c) an incoming second DNA expression cassette which is marker-free, and

f) selecting cell clones obtained after step c) surviving the conditions for negative selection,

g) wherein said positive and negative selection conditions result in recombination frequencies of at least 25%.